REMARKS

Applicants have cancelled claim 25, without prejudice.

The claims stand rejected under 35 U.S.C. 112, first paragraph, for purportedly lacking written description. Applicants respectfully disagree. Applicants have provided a detailed description of the claimed method for the stable and efficient transformation of cardiomyocytes and as such applicant has conveyed to those of skill in the art that they were in possession of the claimed invention at the time of filing.

Currently, Claim 24 recites:

> 24. A method for stable and efficient transformation of cardiomyocytes which comprises:
>
> infusing a recombinant adeno-associated virus (AAV) vector into a coronary artery or a coronary sinus of an animal in an amount of about 1 x 10^5 to about 1 x 10^9 infectious units (IU) AAV per gram body weight and for a time sufficient to stably and efficiently transduce cardiomyocytes perfused through said artery or said sinus, wherein said AAV vector comprises at least one nucleic acid molecule operably linked to a control region, said nucleic acid molecule encoding an angiogenic protein, wherein at least 10% of the cardiomyocytes are transduced with the AAV and the AAV is present in the transduced cardiomyocytes for at least 4 weeks.

For support of this claim, Applicants direct the Examiner's attention to page 9, lines 1-7 wherein applicants describe the amount of rAAV that is suitable for the methods of this invention:

> The amount of rAAV infused into the animal is proportional to the body weight of the animal. Hence in accordance with the invention, stable and efficient transduction occurs when the amount of rAAV infused ranges from about 1x10^5 IU (infectious units) of AAV per gram body weight to about 1x10^9 IU AAV per gram body weight, and preferably, from about 1x10^6 IU AAV per gram body weight to about 1x 10^8 IU AAV per gram body weight, and most preferably 5-6 x 10^7 IU AAV per gram body weight.

Applicants also direct the Examiner's attention to page 8, lines 27-30 wherein applicants teach a time sufficient to stably and efficiently transduce cardiomyocytes by stating:

> The time of infusion contributes to achieving stable and efficient transformation of the cardiomyocytes as well. Thus the infusion time ranges from about 2 minutes to about 30 minutes, more preferably from about 5 minutes to about 20 minutes and most preferably is about fifteen minutes.

Applicants further direct the Examiner's attention to original claims 2, 3 and 4, which recite that in the methods of this invention the rAAV transduces at least 10%, at least 40% or at least 50% of the cardiomyocytes, and to page 8, lines 20-26 wherein applicants describe efficient transduction:

> Alternatively, efficient transduction occurs when at least 10%, and preferably more, of the cardiomyocytes have been transduced, i.e., infected by, the rAAV. By following the methods of this invention and by observing at particular times after transduction ranging over a few to many weeks, about 25%, about 40% or even about 50% of the cardiomyocytes will be transduced.

Applicants further direct the Examiner's attention to page 11, lines 19-21 wherein applicants disclose: "By 4 weeks after perfusion, 40% of the cardiomyocytes were β-gal positive."

See also Figure 2, which demonstrates the stable and efficient transduction of the cardiomyocytes wherein at least 40% (and thus at least 10% as recited in original claim 2) of the cardiomyocytes are transduced at 4 weeks and at 8 weeks.

Furthermore, applicants' have provided a working example that demonstrates that the disclosed method produces the desired results. On page 11, Applicants demonstrate the stable and efficient transduction of cardiomyocytes in C57BL/6 mice hearts explanted and perfused

with 1.5 x 10^9 IU of AAV CMV-LacZ. Those of skill in the art appreciate that adult C57BL/6 mice weigh on average about 25-30 grams and thus the amount of virus in applicants' Example is approximately 5 x 10^7 IU per gram body weight, which falls within the range of "1 x 10^5 to about 1 x 10^9 infectious units (IU) AAV per gram body weight" as recited in applicants' claims. Figure 2 demonstrates that β-gal is expressed stably and efficiently in the cardiomyocytes of the perfused heart at four and eight weeks.

In view of the foregoing, it is clear that applicants have provided sufficient description of the invention as claimed to satisfy the requirement of 35 U.S.C. 112, first paragraph. Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims.

Claims 24-30, 32, 33, 35-40, 43 and 45 stand rejected under 35 U.S.C. 112, first paragraph for purportedly lacking an enabling disclosure. Applicants respectfully disagree.

The Examiner has used the failures of the prior art to contend that applicants' invention is not enabled and states "it appears that the state of the art at the time of the invention held that the transduction efficiency of cardiomyocytes by AAV vector via intracoronary artery injections in an animal was pretty low (about 0.2% with 5 x 10^7 AAV units injected.)" It is clear from the Examiner's comments that the prior art did not enable applicants' invention. However, applicants have provided sufficient teaching for one of skill in the art to achieve stable and efficient transformation of cardiomyocytes with rAAV.

As mentioned by applicants in their amendment filed 6-15-05, Kaplitt et al. 1996 fails to teach the invention as claimed. Kaplitt failed to teach the amounts of rAAV to administer, as taught by applicants, and Kaplitt failed to teach infusion methods sufficient to achieve stable and

efficient transduction and, ultimately, Kaplitt failed to obtain stable and efficient transduction of cardiomyocytes. Kaplitt also failed to provide sufficient guidance for one of skill in the art to practice applicants' invention and therefore Kaplitt is not enabling for applicants' invention. Furthermore, Kaplitt's failure demonstrates that the state of the art prior to applicants' invention was such that one of skill in the art could not achieve stable and efficient transduction.

In contrast, applicants successfully achieved stable and efficient transduction of cardiomyocytes and taught one of skill in the art how to practice their invention without having to resort to undue experimentation.

The Examiner contends:

> The specification only discloses perfusion with $1.5x10^9$ IU of AAV CMV-LacZ for 15 minutes at 4°C and by 4 weeks after perfusion about 40% of the cardiomyocytes were β-gal positive. It is unclear how many IU AAV/gram body weight corresponds to $1.5x\ 10^9$ IU of AAV CMV-LacZ used. (Office Action page 6) (emphasis added).

Applicants respectfully disagree. The specification only exemplifies perfusion with $1.5x10^9$ IU of AAV CMV-LacZ, but it discloses much more:

> The amount of rAAV infused into the animal is proportional to the body weight of the animal. Hence in accordance with the invention, stable and efficient transduction occurs when the amount of rAAV infused ranges from about 1×10^5 IU (infectious units) of AAV per gram body weight to about $1x10^9$ IU AAV per gram body weight, and preferably, from about $1x10^6$ IU AAV per gram body weight to about $1x\ 10^8$ IU AAV per gram body weight, and most preferably $5\text{-}6 \times 10^7$ IU AAV per gram body weight.
>
> Specification page 9, lines 1-7

While the specification may exemplify an infusion of "15 minutes at 4°C" it discloses:

> The time of infusion contributes to achieving stable and efficient transformation of the cardiomyocytes as well. Thus the infusion time ranges from about 2 minutes to about 30 minutes, more preferably from about 5 minutes to about 20 minutes and most preferably is about fifteen minutes.
>
> Specification page 8, lines 27-30

And while the Examiner states: " It is unclear how many IU AAV/Gram body weight corresponds to 1.5x 10^9 IU of AAV CMV-LacZ used ..." those of skill in the art appreciate that the average adult C57BL/6 mouse weighs about 25-30g and thus one of skill in the art would readily recognize that the amount of rAAV that is used in the example is well within the range specified in applicants' claims. (The hearts were explanted from C57BL/6 mice and perfused with $1.5x10^9$ IU of AAV CMV-LacZ: this total amount of virus which divided by 25-30 gram body weight is approximately $5\text{-}6x10^7$ IU/gram body weight.) One of skill in the art could equally as easily determine the amount of rAAV to infuse into other subjects' hearts based on their body weight and readily determine the infusion time to achieve stable and efficient transformation of cardiomyocytes by following the teachings of applicants' specification. Thus, one of skill in the art using the knowledge available to such person and the disclosure of applicants' patent document could readily make and use the invention without undue experimentation. *Northern Telecom, In. v. Datapoint Corp.*, 15 USPQ 1321, 1229 (It is not fatal if some experimentation is needed for the patent document is not intended to be a production specification.)

Applicants have taught the factors that influence successful transformation, applicants have taught a particular range of rAAV to use and the range is based upon the body weight of the animal. Applicants have also taught the time of infusion that is sufficient to achieve stable and

efficient transduction. Applicants have demonstrated, with an actual working example even though one is not required, that by following applicants' teachings, efficient and stable transduction of at least 10% of the cardiomyocytes is achieved (Figure 2 demonstrates at least 10% of the cardiomyocytes are transduced, and in fact at least 40% are transduced). One of skill in the art following applicants' disclosure could readily repeat applicants' methods as currently claimed to obtain the results produced by those methods. As such, applicants have satisfied the enablement requirement of 35 U.S.C. 112, first paragraph and respectfully request that the Examiner reconsider and withdraw the rejection of the claims.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. WO-BSX 234 US1/10408799 from which the undersigned is authorized to draw.

Dated: October 17, 2005

Respectfully submitted,

By Mary Anne Schofield

Mary Anne Schofield
Registration No.: 36,669
FULBRIGHT & JAWORSKI L.L.P.
801 Pennsylvania Avenue, N.W.
Washington, DC 20004-2623
(202) 662-0200 (Telephone)
(202) 662-4643 (Fax)
Attorney for Applicant